Wnt Signaling Pathway

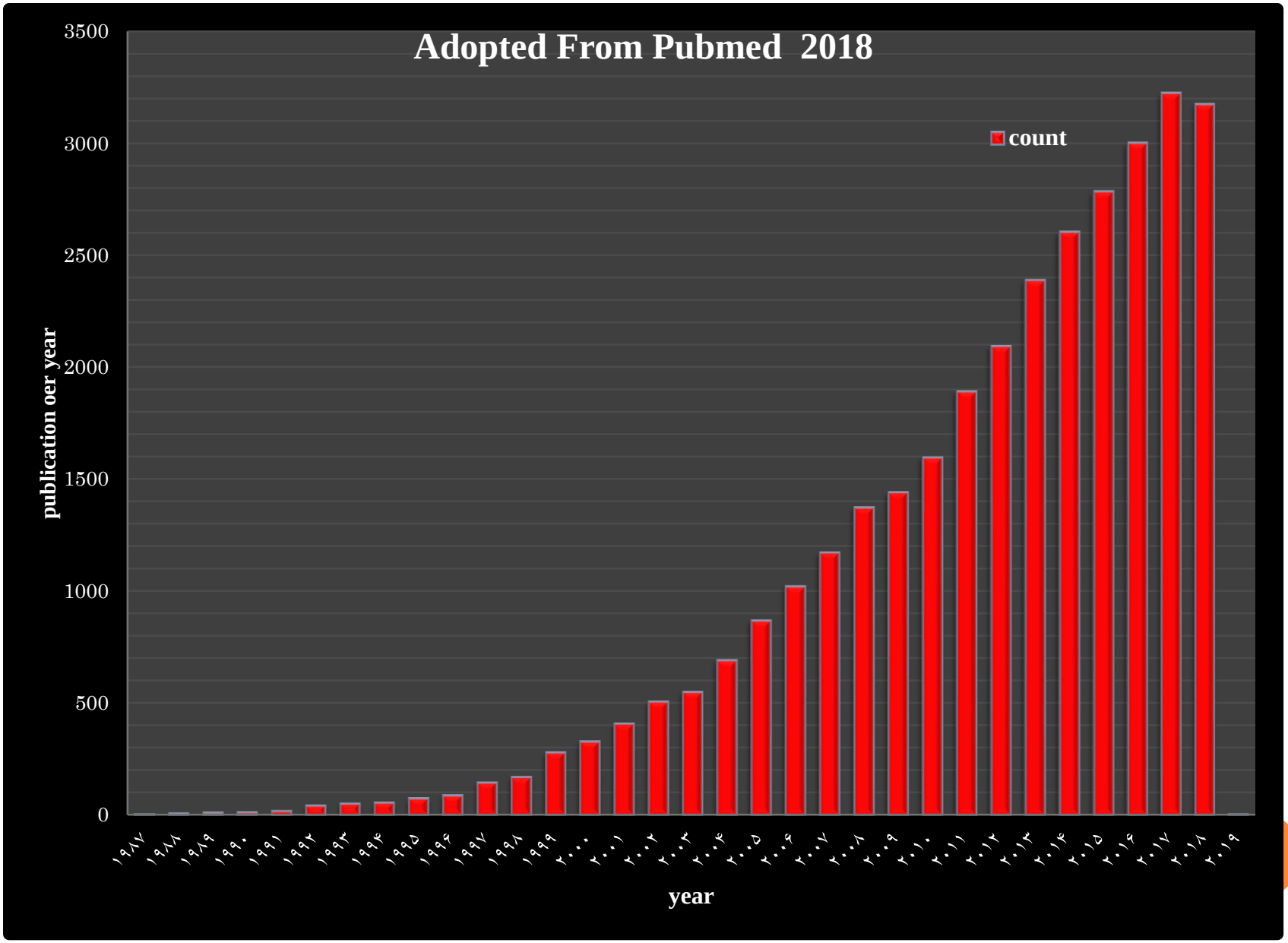
Presented by: Leila Soufi

M.Sc Student of Medical Biotechnology
Paramedical Sciences Faculty

Qazvin University of Medical Sciences

Supervisor: Dr.Gheibi

2018


Adopted From Pubmed 2018
count
publication oer year
year
3500
3000
2500
2000
1500
1000
500
0
١٩٨٧
١٩٨٨
١٩٨٩
١٩٩٠
١٩٩١
١٩٩٢
١٩٩٣
١٩٩٤
١٩٩٥
١٩٩٦
١٩٩٧
١٩٩٨
١٩٩٩
٢٠٠٠
٢٠٠١
٢٠٠٢
٢٠٠٣
٢٠٠٤
٢٠٠٥
٢٠٠٦
٢٠٠٧
٢٠٠٨
٢٠٠٩
٢٠١٠
٢٠١١
٢٠١٢
٢٠١٣
٢٠١٤
٢٠١٥
٢٠١٦
٢٠١٧
٢٠١٨
٢٠١٩

“List of Contents”

Introduction

Introduction

“Wnt signal transduction” cascade consists of various proteins (14)

- **A family of cysteine-rich secreted glycoproteins.**
- **19 mammalian Wnt proteins have been identified to fall into 12 conserved Wnt subfamilies.**
- **Binding to 10 different Frizzled receptor and other co-receptors.**

- **Acylation (on cysteine residues 77 & 209) and N-glycosylation (on Asn103 and Asn414 residues) are Wnt Post-translational modifications that are accomplished by acyltransferase porcupine (located in ER).**

Introduction

Wnt signal transduction Roles

"Wnt signal transduction play roles in embryonic & adult stages in human and animals (8, 10 , 11, 17):

- **Evolution**
- **Cell proliferation, growth & differentiation**
- **Cell survival, stem cell renewal & organ formation.**

- **Wnt pathway components are "directional growth factor" (induce cell proliferation, and both primary formation & maintenance of tissue exact shape (8).**

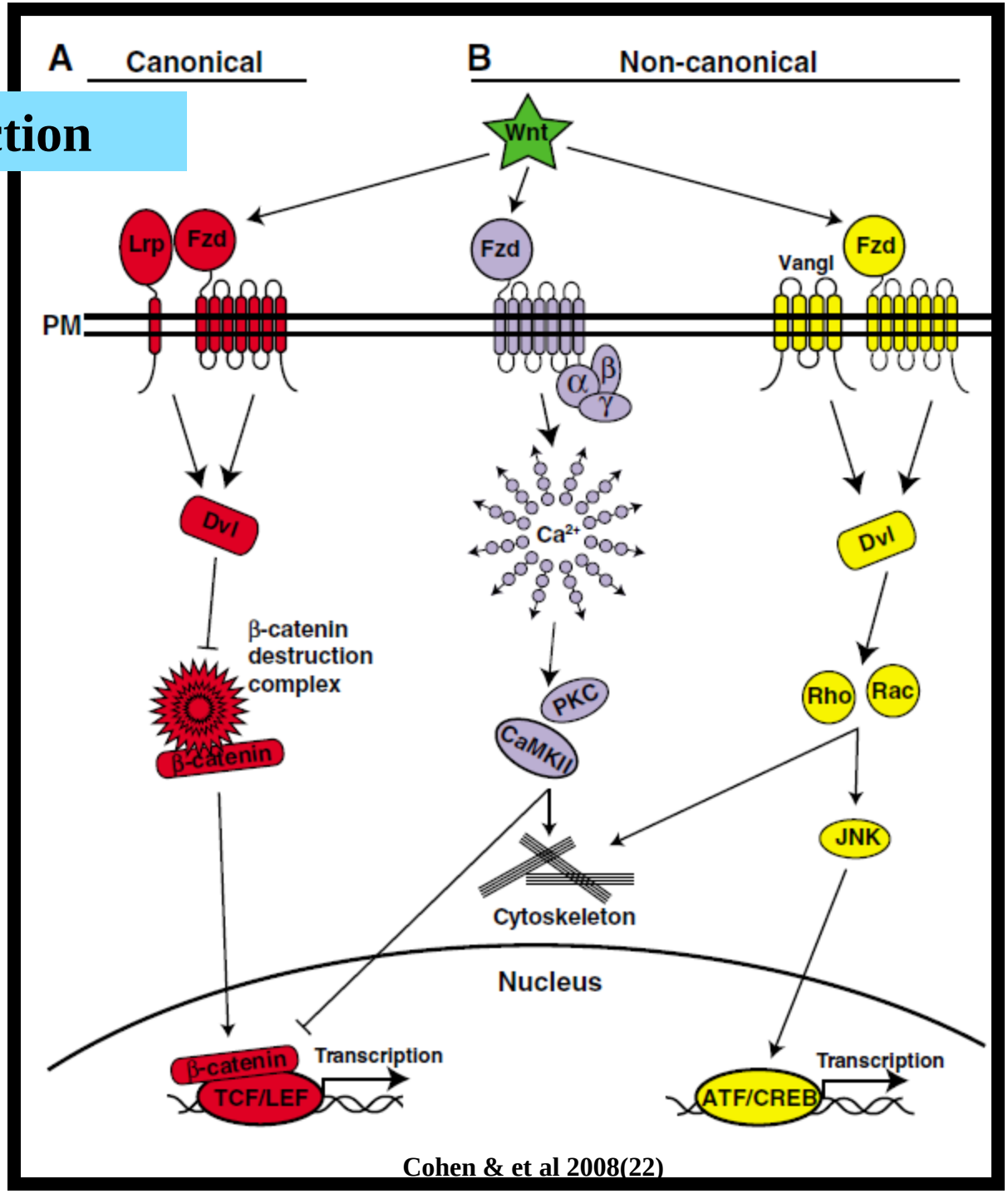
Introduction

- **Signal transduction 3 pathways:**

- **1.Canonical pathway**
- **2.Non-canonical planar cell polarity pathway**
- **3.Non-canonical Wnt/calcium pathway (8).**

- **Wnt pathway component mutation may be cause to some pathological conditions such as cancer (10).**

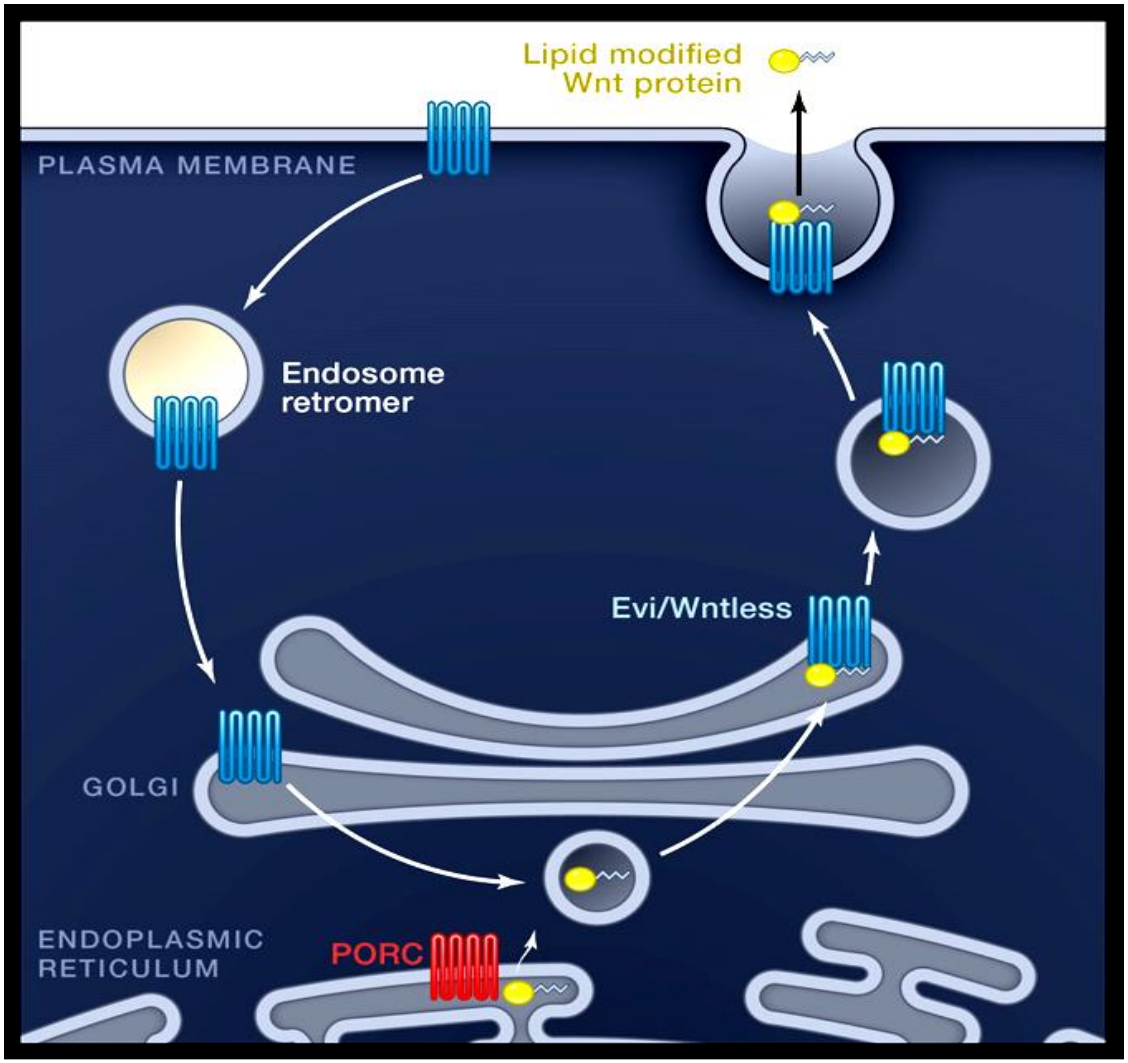
Introduction



Cohen & et al 2008(22)

Introduction

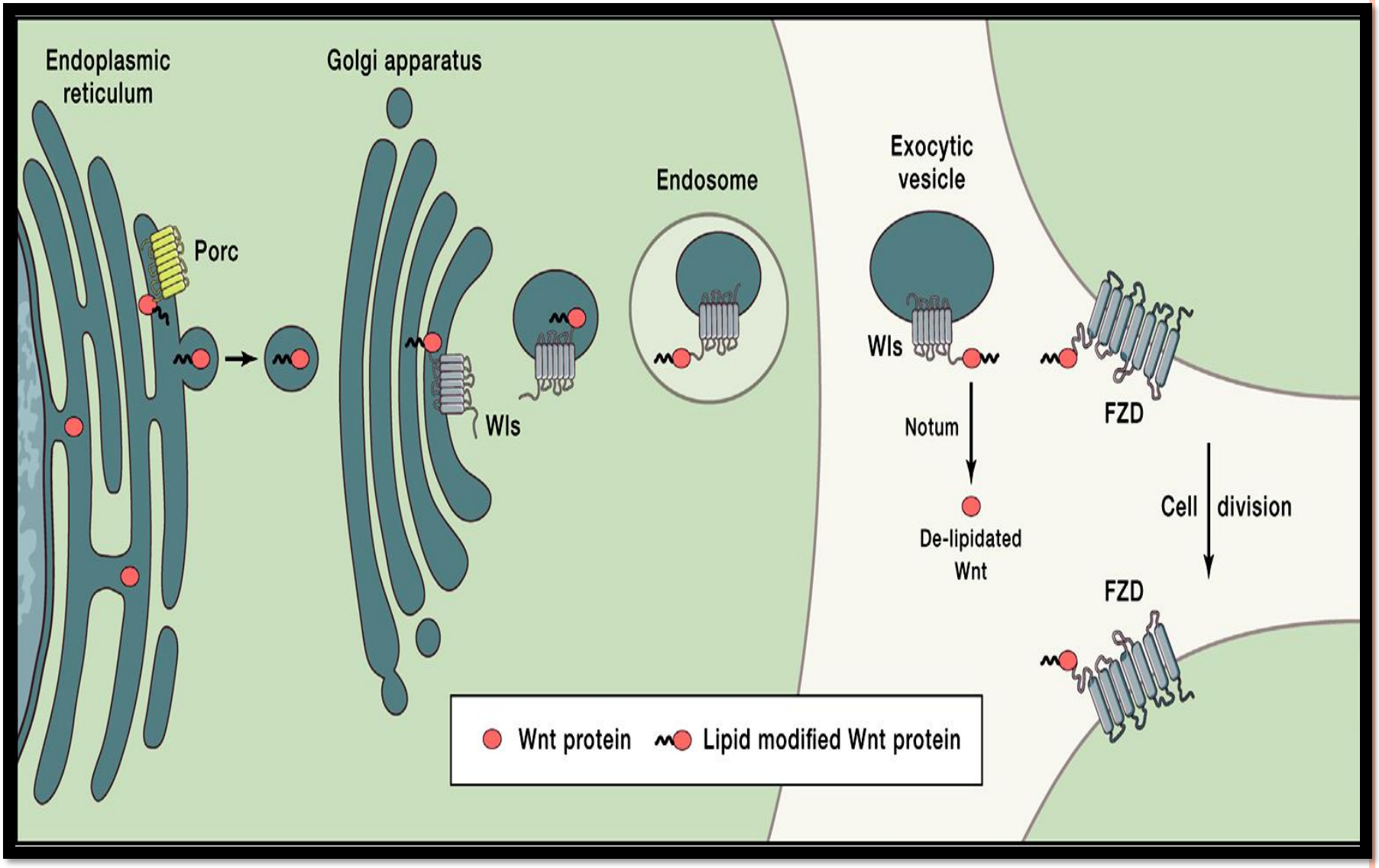
The Wnt Secretion Machinery



Clevers & Nusse& 2012(4)

Introduction

Model of Wnt Secretion



Nusse& Clevers 2017(2)

Model of Wnt Secretion

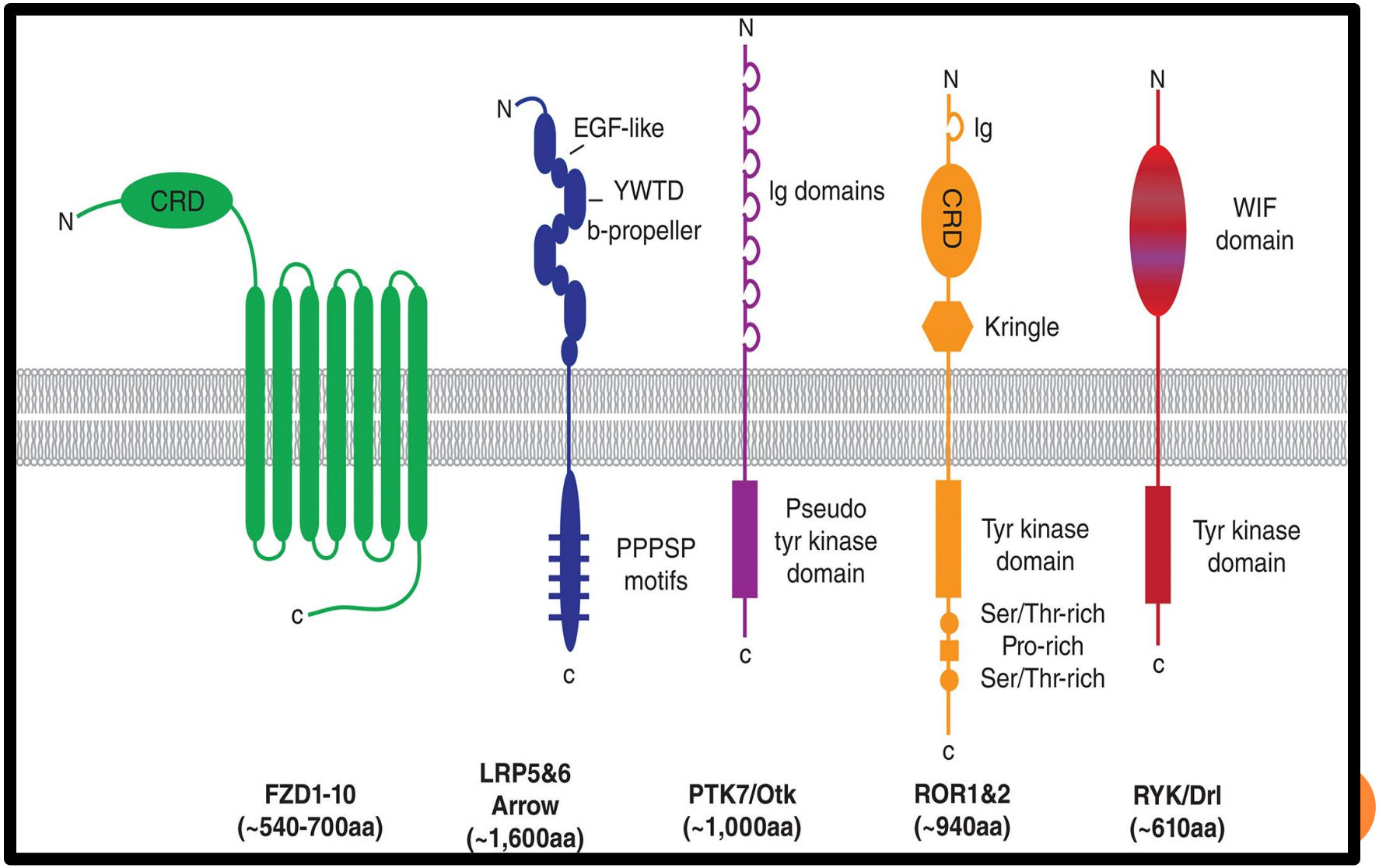
- **"Wnt" is a cysteine-rich 40kD protein, that is attached to a palmitoleic acid (an acyl group) before its secretion from cells.**

- **Wnt is acylated when it is inside the cell.**
- **This acyle group facilitates Wnt passing through the cell membrane and binding to its receptors (10)**

- **Notum enzyme (a deacylase) can remove acyl group and deactivate the Wnt. Deacylated Wnt can not attach to its receptor (10, 16).**

Introduction

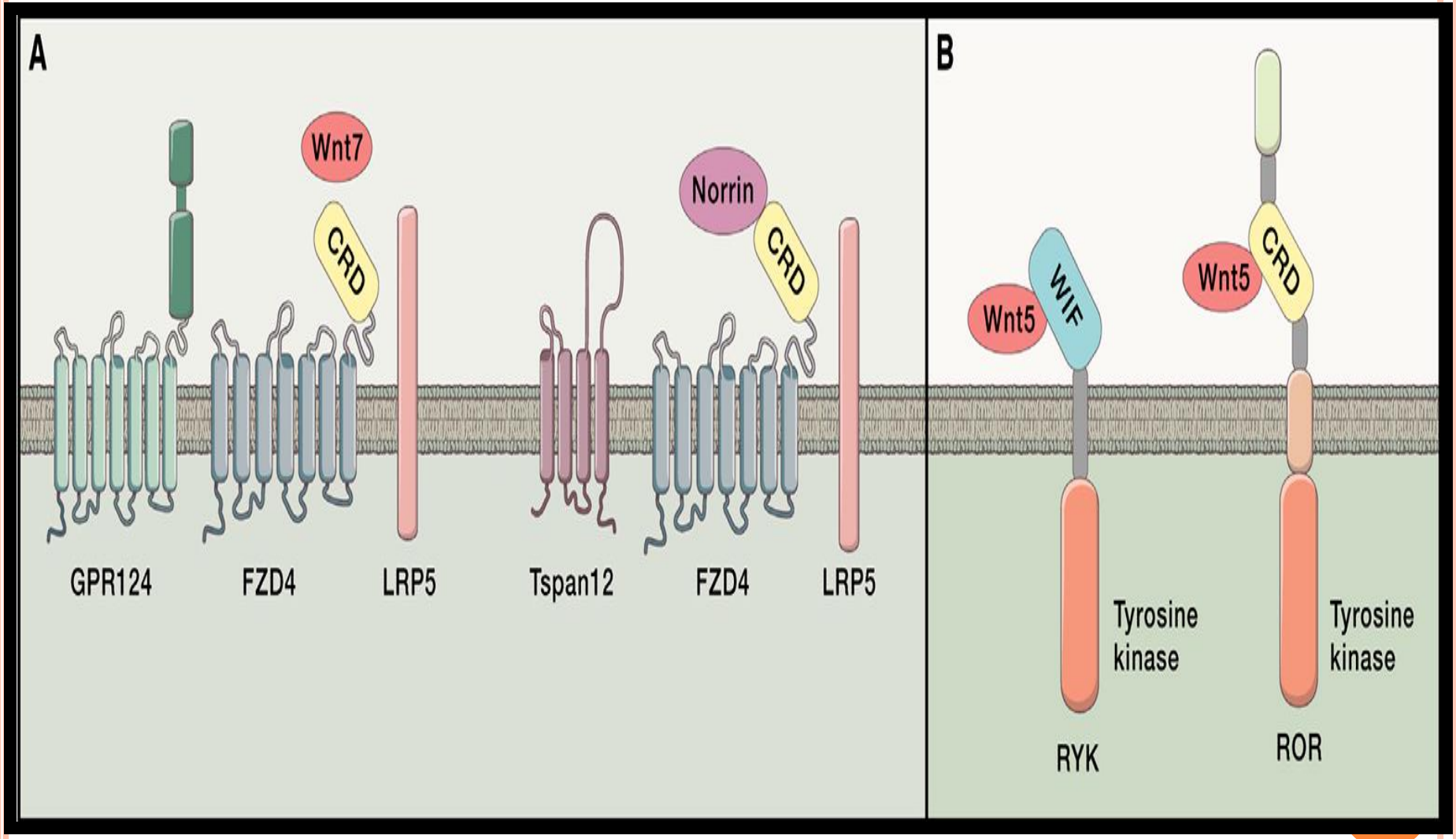
Wnt Receptors



http://wires.wiley.com/WileyCDA/WiresArticle/wisId-WSBM1422.html(21)

Introduction

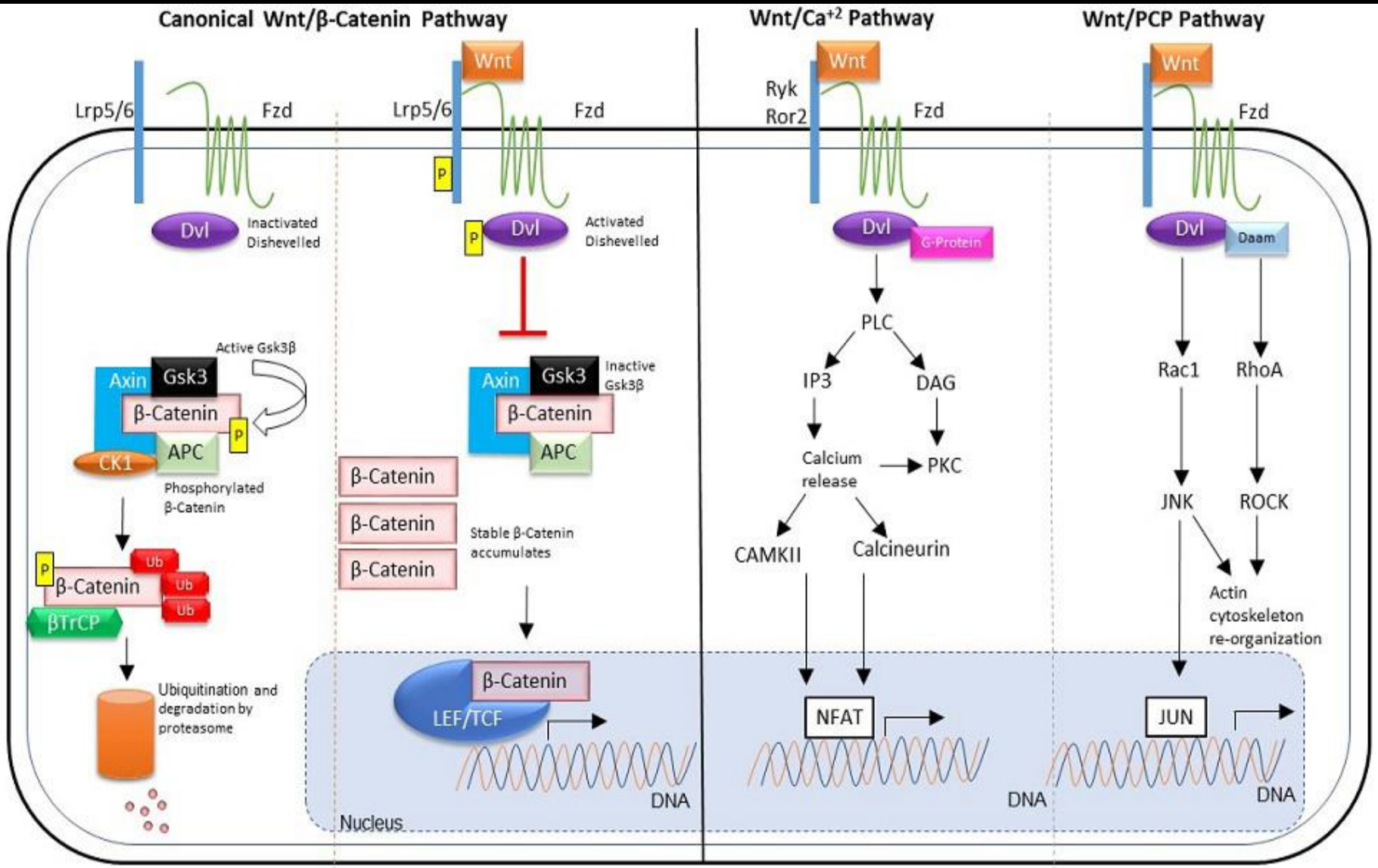
Wnt Receptors



Nusse& Clevers 2017(2)

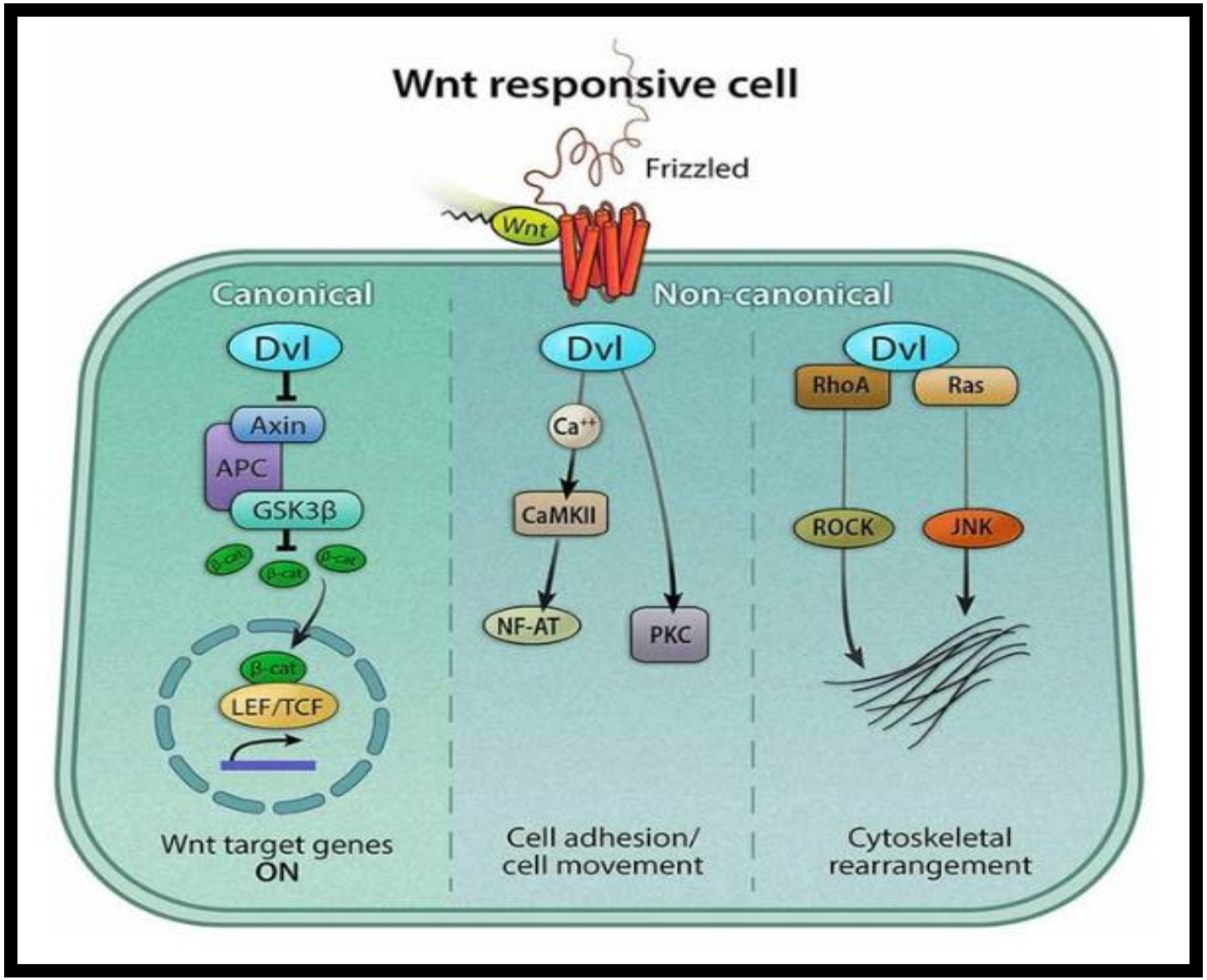
Wnt Signaling

Wnt Signaling



Garcia, 2018(23)

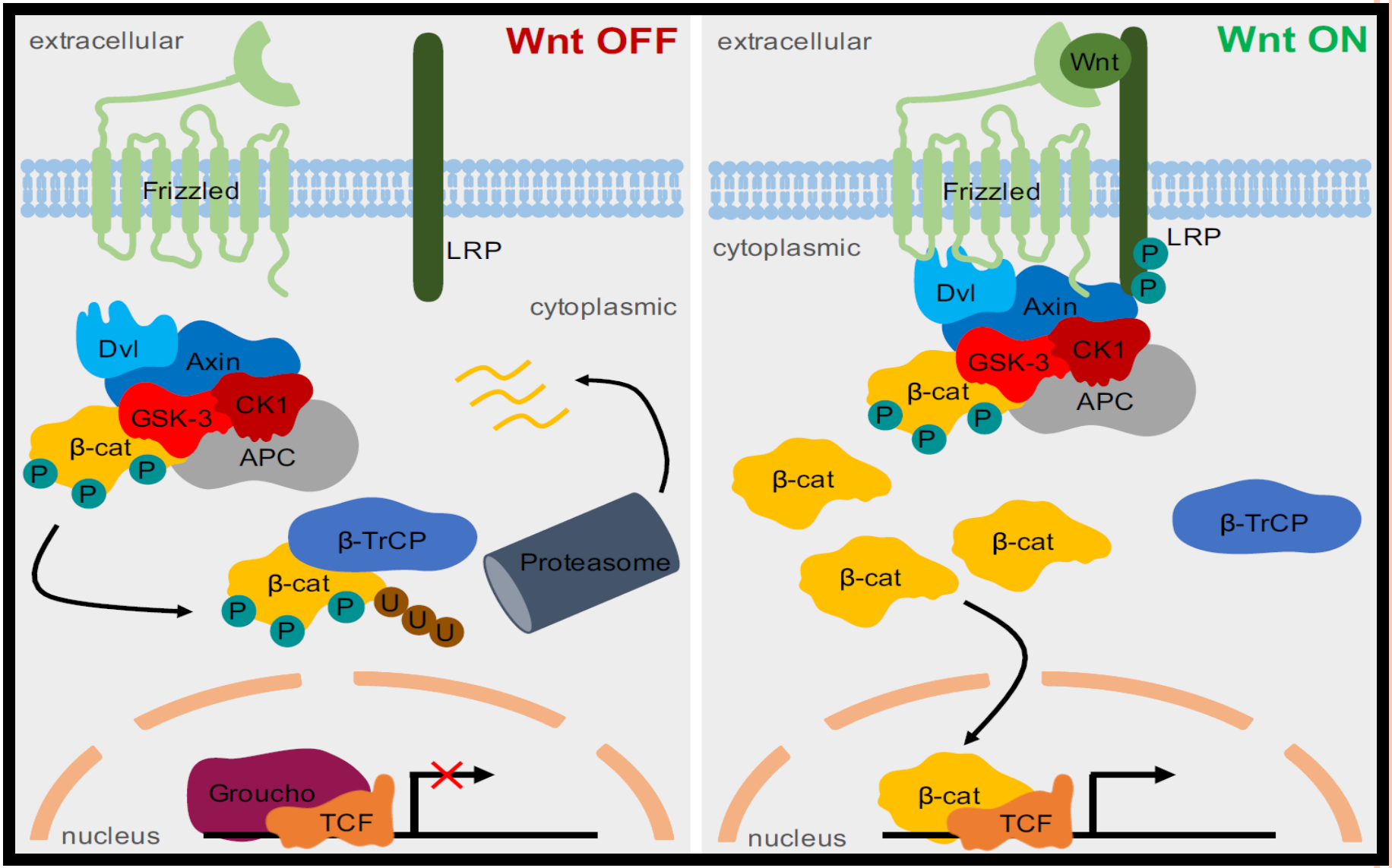
Wnt Signaling



Jansson & etal 2015(24)

Wnt Signaling

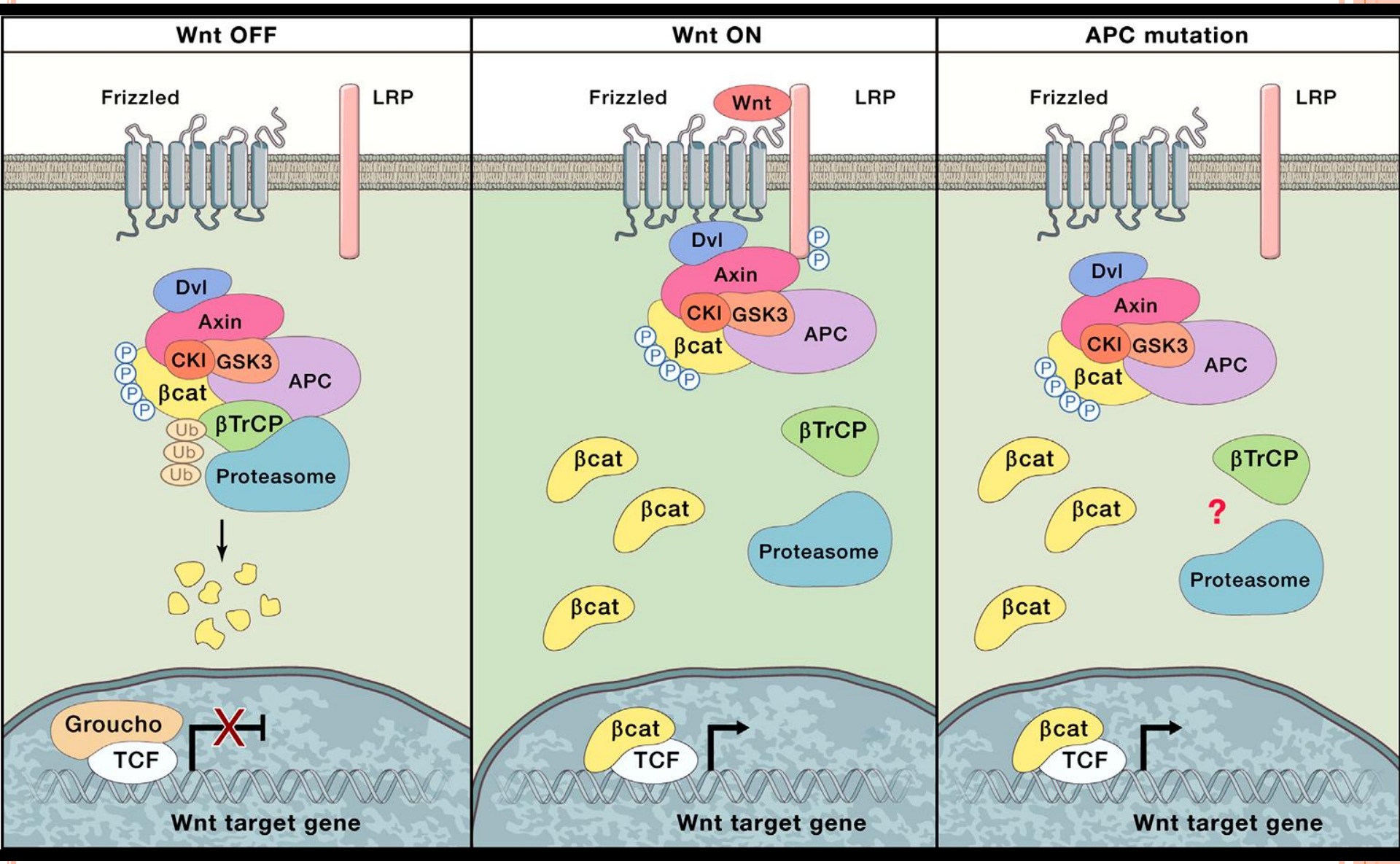
Canonical Wnt signaling



Kretzschmara & Cleversa 2017(3)

Wnt Signaling

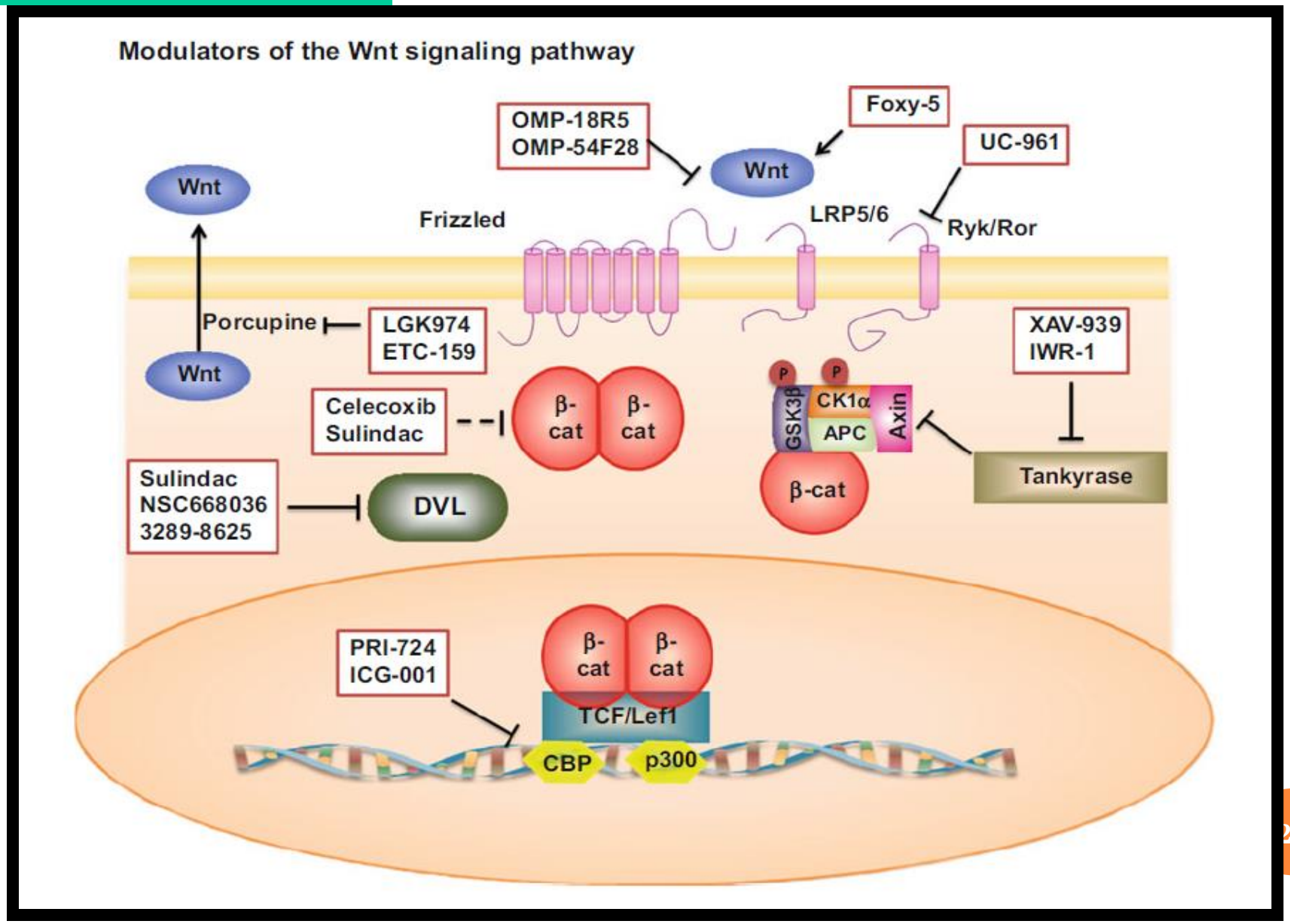
Wnt Signaling in Cells



Nusse& Clevers 2017(2)

Wnt Inhibition

Wnt Inhibition



Duchartre et al. 2017(5)

Wnt Inhibition

Small-Molecule to activate or inhibite Wnt signaling

Table 2. Small Molecules to Activate or Inhibit Wnt Signaling

Compound	Target	Inhibitor/Activator of the Target	Effect on Wnt Signaling	Reference
IWP	Porcupine	inhibitor	inhibits	Chen et al., 2009
LGK974	Porcupine	inhibitor	inhibits	Kulak et al., 2015
C59	Porcupine	inhibitor	inhibits	Proffitt et al., 2013
Apicularen and bafilomycin	vacuolar ATPase	inhibitor	inhibits	Cruciat et al., 2010
XAV939	tankyrase Axin	activates Axin	inhibits	Huang et al., 2009
IWR	tankyrase, Axin	activates Axin	inhibits	Kulak et al., 2015
G007-LK, G244-LM	tankyrase, Axin	activates Axin	inhibits	Lau et al., 2013
IQ1	PP2A	activator	activates	Miyabayashi et al., 2007
QS11	ARFGAP1	activator	activates	Zhang et al., 2007
SB-216763	GSK3	inhibitor	activates	Coghlan et al., 2000
CHIR99021	GSK3	inhibitor	activates	Ying et al., 2008
BIO (6-bromoindirubin-3′-oxime)	GSK3	inhibitor	activates	Sato et al., 2004
L807mts	GSK3	inhibitor	activates	Licht-Murava et al., 2016
LY2090314	GSK3	inhibitor	activates	Atkinson et al., 2015
ICG-001	CREB-binding protein	inhibitor	inhibits	Emami et al., 2004

Based on http://web.stanford.edu/group/nusselab/cgi-bin/wnt/smallmolecules.

Nusse& Clevers 2017(2)

Wnt Inhibition

Selected Wnt pathway inhibitors & their use in mouse tumor models

Compound name	Mode of action	Tested applications	Publications for *in vivo* inhibitor use if applicable
Lgk974	Inhibits Porcupine	Cell lines, div. murine cancer models, phase 1 clinical trial	Liu *et al.*, 2013 Clinical trial identifier: NCT01351103
ETC-159	Inhibits Porcupine	Rspo3 translocations in CRC xenografts	Madan *et al.*, 2016
Wnt-C59	Inhibits Porcupine	Cell lines, murine cancer models	Proffitt *et al.*, 2013
IWP-2	Inhibits Porcupine	Murine keratoacanthoma model, cell lines	Zito *et al.*, 2014
Xav939	Tankyrase 1 + 2	Cell lines, xenografts	Huang *et al.*, 2009, Arques *et al.*, 2016
ICG-001	Inhibits β-catenin- CBP interaction	Diverse murine tumour models	Emami *et al.*, 2004
PRI-724 (2nd generation of ICG- 001)	Inhibits β-catenin- CBP interaction	Clinical trial phase 1	Clinical trials identifier: NCT01764477, NCT01606579
OMP-18R5 (mAB)	Antibody against FZD receptors	Various xenograft models, clinical trial phase 1	Gurney *et al.*, 2012 Clinical trials identifiers: NCT01973309, NCT01345201
OMP-54F28 (Fzd8-Fc fusion)	Competes with FZDs for Wnts	Various xenograft models, clinical trial phase 1	Wei *et al.* 2011 Clinical trial identifier: NCT02092363
FJ9	Inhibits Dishevelled PDZ domain interaction with FZD	Cell lines, xenograft models	Fujii *et al.* 2007
SAH-BCL9	Inhibits Bcl9-β-catenin interaction	Cell lines, xenograft models	Takada *et al.*, 2012
1,4-Dibenzoylpiperazines	Inhibits Bcl9-β-catenin interaction	Cell lines	Wisniewski *et al.*, 2016

Zimmerliet al. 2017(7)

Wnt Inhibition

Wnt inhibitors currently in clinical trials

Clinical trials	Disease	Mechanism	Ref
OMP18R5, Vantictumab	Solid tumors	Humanized Ab against multiple Fzd receptors	[74]
OMP-54F28, Fzd8-Fc	Pancreatic, Ovarian, Hepatocellular, Colorectal, and Breast	Fc fusion protein with Fzd8, which binds all Wnt ligands	[75]
PRI-724	Solid Tumors, Colon and Pancreatic Cancer, CML and AML	Small molecule inhibitor of CBP/ catenin binding	[76]
LGK974, Porcupine inhibitor	Melanoma, Breast cancer, and Pancreatic adenocarcinoma	Wnt posttranslational acylation and palmitoylation	[77]
ETC-1922159 (ETC-159), Porcupine inhibitor	Colon, Ovarian, and Pancreas cancers	Wnt posttranslational acylation and palmitoylation	[78]
UC-961 (cirmtuzumab)	Chronic Lymphoid Leukemia	Humanized antibody against ROR1	[79]
Foxy-5	Breast, Colon, Prostate	Reduced cell migration through Fzd-5 and cytosolic calcium signal	[80]

This table summarizes the different Wnt pathway modulators with variable specificities and at different stages of development (fully described in the main text)

Duchartre et al. 2017(5)

Wnt & Related Diseases

Status of Wnt Pathway Drug Discovery Approaches

	Institution	Drug Type	Target	Stage
Wnt/receptor interactions	Genentech	Soluble Receptor Biolgic	Wnt ligands	Discovery
	UCSF	Antibody	Wnt1, Wnt2	Discovery
	OncoMed	Antibody	Fzds	Phase I 2011
Cytosolic Signaling	St. Jude Children's Res. Hospital	Small Molecule	Dvl	Discovery
	Novartis	Small Molecule	Tankyrase 1,2	Discovery
	UTSW	Small Molecule	Axin	Discovery
	UTSW	Small Molecule	Porcupine	Discovery
	Theriac Pharmaceutical	Small Molecule	β-catenin	Phase I 2010
	Fate Therapeutics	Small Molecule	Unknown	Phase I
Nuclear Signaling	Harvard/Novartis	Small Molecule	TCF/β-catenin	Discovery
	USC	Small Molecule	CBP	Discovery

Curtin & Lorenzi 2017 (12)

Wnt Inhibition

Wnt inhibitors clinically approved

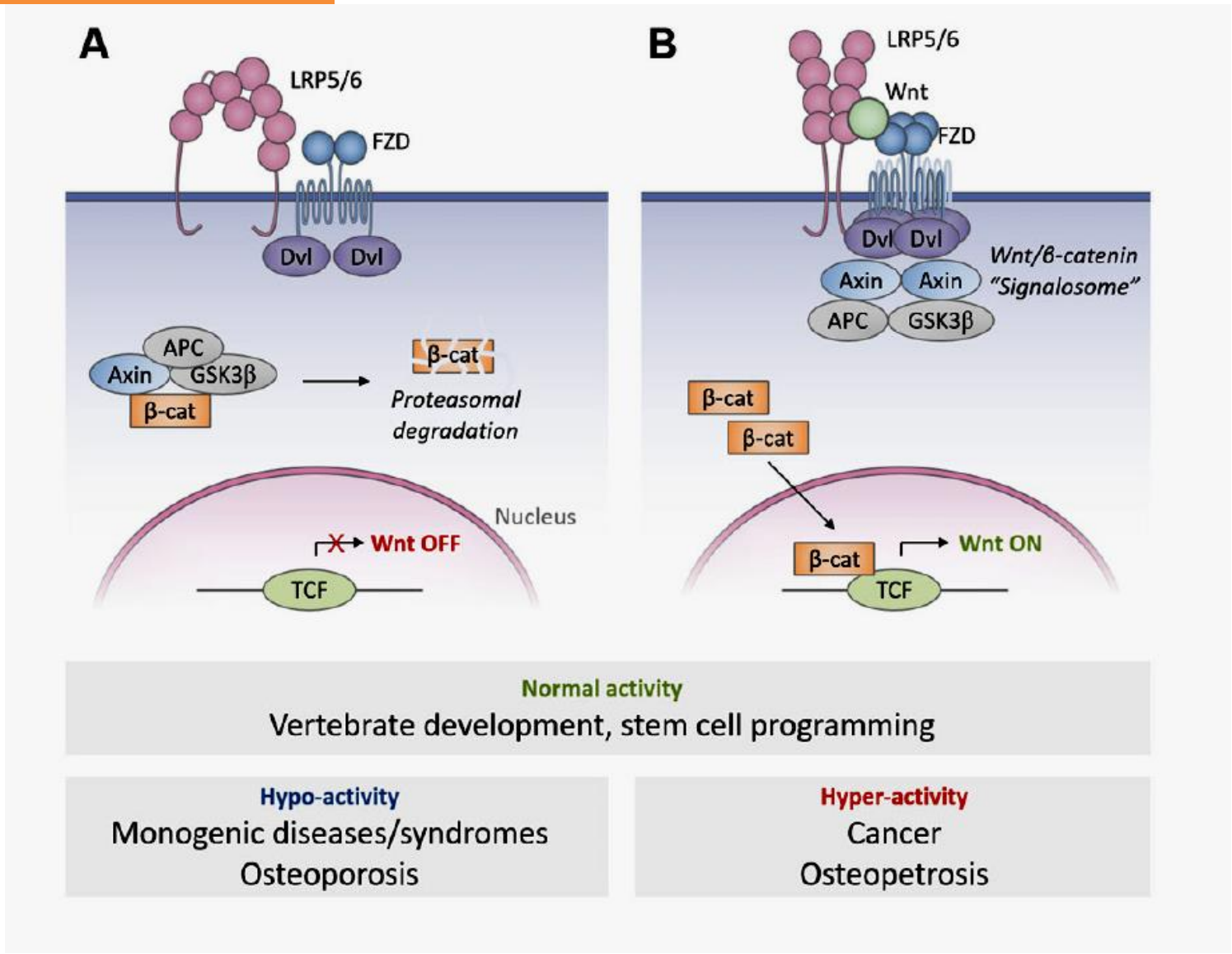
Clinical	Disease	Mechanism	Ref
NSAID (Aspirin, Celecoxib)		PGE2 generated via COX suppresses β-catenin degradation	[66–69]
Retinoids	APML	Unclear	[99]
Vitamin D	Colorectal and breast cancers	Unclear	[70]
Pyrvinium pamoate	Lung cancer, colon cancer	Unclear: Wnt signaling inhibition via CK1α activation or GSK3 activation	[72]
Sulindac		Dishevelled inhibition	[73]

This table presents the nonspecific Wnt inhibitors that are already clinically approved. The mechanism of action of these drugs (when it is known) involves the inhibition of different intracellular proteins implicated in the Wnt signaling pathway (β-catenin, CK1α, GSK3β, and Dvl)

Duchartre et al. 2017(5)

Wnt & Related Diseases

Wnt & Related Diseases



Normal activity

Vertebrate development, stem cell programming

Hypo-activity

Monogenic diseases/syndromes

Osteoporosis

Hyper-activity

Cancer

Osteopetrosis

DeBruine & etal. 201٧(٩)

Wnt & Related Diseases

Wnt is one of the "cancer-related signaling pathways" which its abnormal expression was observed in many cancers such as (11,8)

- **Lung**
- **Breast**
- **Ovarian**
- **hematopoietic malignancies**
- **Especially hepatocellular carcinoma & (colorectal(18,19)) cancer.**

Wnt & Related Diseases

- **Wnt1 is a sign of tumor metastasis(11).**

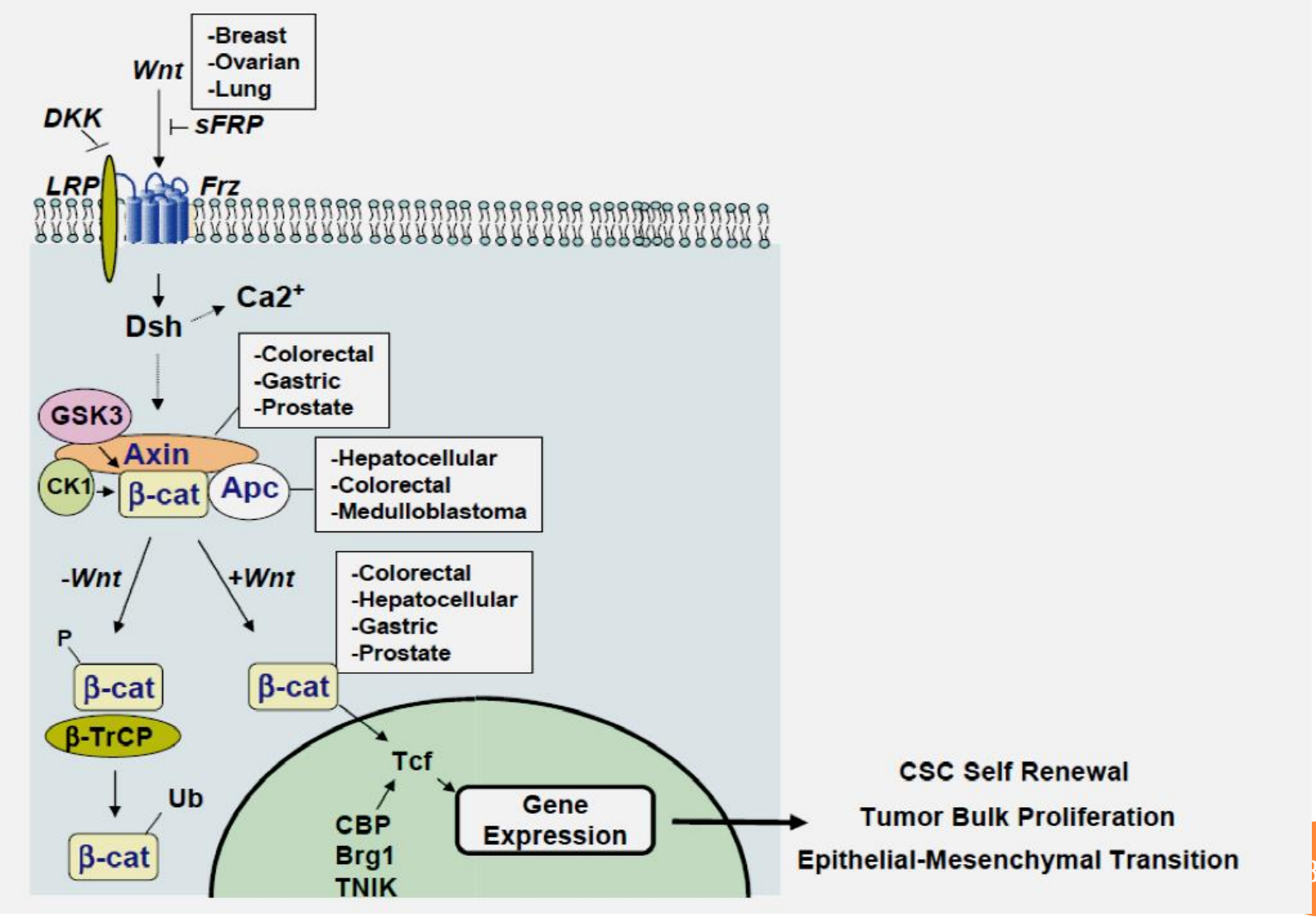
- **Wnt3a over-expression relates with MMP-9 level in colorectal cancer (11).**

  & by decrease in β-catenin acetylation & increase the cytosolic β-catenin can increase the MCF-7 cells proliferation (11,12).

- **Wnt signaling can play roles in cancer stem cell (CSCs) activities ➔ drug resistance & cancer metastasis in various cancers (colon, breast and cutaneous) (12).**

Wnt & Related Diseases

Canonical Wnt signaling and dysregulation in cancer.

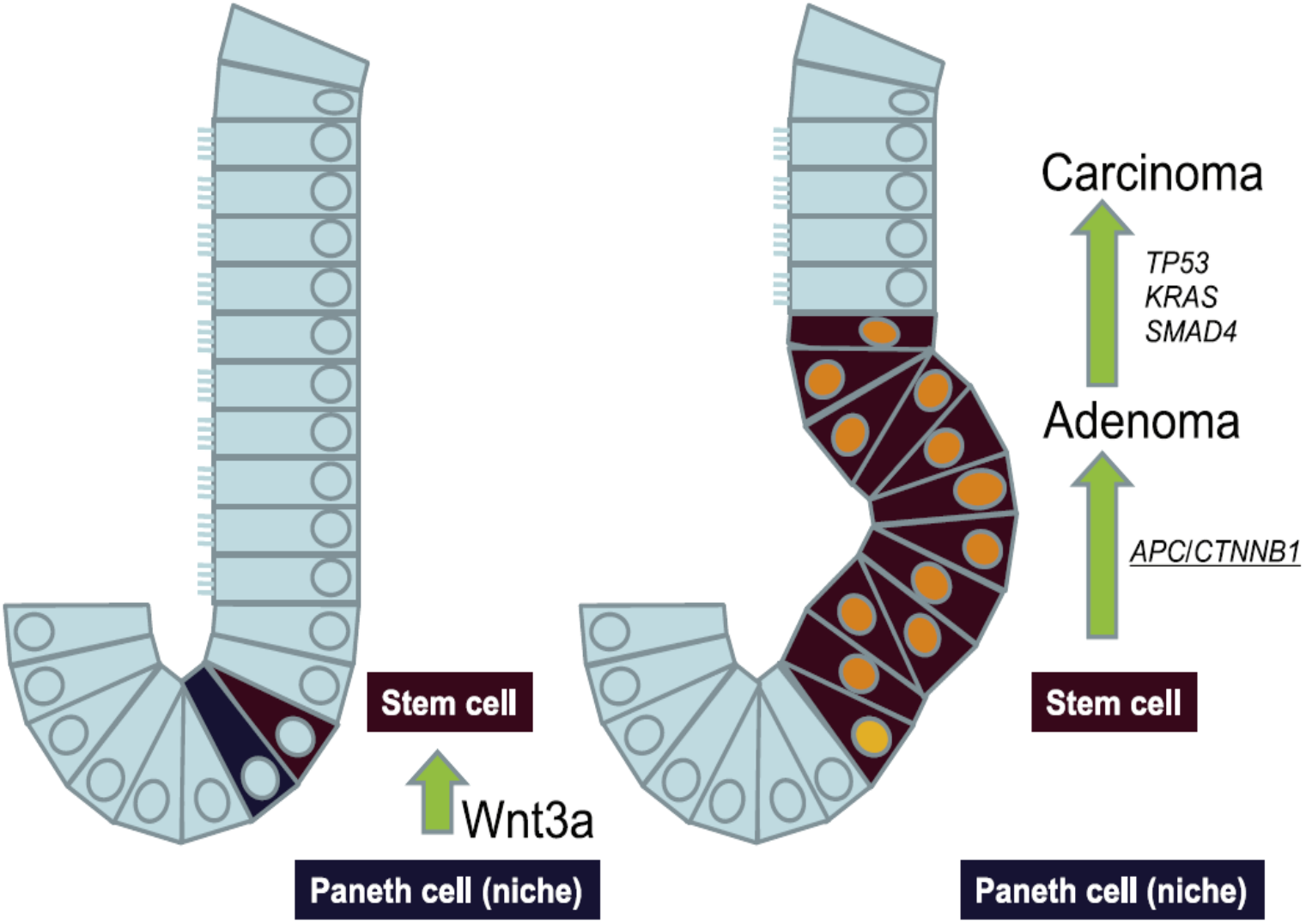


Curtin & Lorenzi 2017 (12)

Wnt & Related Diseases

- **More than 90% of colorectal cancers occurred because of at least one mutation in Wnt signaling pathway genes.**
- **Wnt3 can increase stem cells number in normal intestinal epithelial tissue.**
- **In colorectal cancer, APC or CTNNB1 mutation ➔ Wnt signaling activation➔ intestinal epithelial stem cell transformation into adenoma➔ carcinoma (via some other genes alterations such as SMAD4, KRAS, and TP53 genes).**
- **Other Wnt signaling pathway genes which altered in colorectal cancer are: FZD10, T-cell factors-3 and -4 (TCF3/4) (TCF7L1/2), axis inhibitor 2 (AXIN2) (13).**

Wnt & Related Diseases



Masuda etal.2015 (13).

Wnt & Related Diseases

Table 1. Diseases Associated with Wnt Signaling Components

Disease	Gene	Reference
Bone density defects	LRP5	Gong et al., 2001; Little et al., 2002; Boyden et al., 2002
	LGR4	Styrkarsdottir et al., 2013
	SOST	Brunkow et al., 2001; Balemans et al., 2001
	WNT16	Zheng et al., 2012
	WNT1	Pyott et al., 2013
	WTX	Jenkins et al., 2009
Familial exudative vitreoretinopathy	LRP5	Toomes et al., 2004
	FZD4	Robitaille et al., 2002
	Norrin	Xu et al., 2004
	TSPAN12	Poulter et al., 2010
Robinow syndrome	WNT5A	Person et al., 2010
	DVL1	White et al., 2015
	ROR2	van Bokhoven et al., 2000
Tooth development defects	LRP6	Massink et al., 2015
	WNT10A	Adaimy et al., 2007
	WNT10B	Yu et al., 2016
	AXIN2	Lammi et al., 2004

Based on http://web.stanford.edu/group/nusselab/cgi-bin/wnt/human_genetic_diseases (selected for diseases with multiple pathway components implicated).

Nusse& Clevers 2017(2)

Wnt & Related Diseases

Table 1. Human diseases related with the Wnt/β-catenin signaling pathway

Disease	Wnt/β-catenin signaling pathway componetnt	Reference
Cancer	APC	18, 19
	β-catenin	15, 18
	axin1	20, 21
	axin2	22
FAP	APC	16, 17
Tooth agenesis	axin2	23
Bone disease (high or low bone mass)	LRP 5	33 – 37
OPPG	LRP 5	33
FEVR	LRP 5	38, 39
Vascular calcification	unknown	45
Cardiac hypertrophy	GSK-3β	50 – 52

APC, adenomatous polyposis coli; FAP, familial adenomatous polyposis; LRP, low-density lipoprotein receptor-related protein; OPPG, osteoporosis-pseudoglioma syndrome; FEVR, familial exudative vitreoretinopathy; GSK-3β, glycogen synthase kinase-3β.

Yanaga & Sasaguri 2007(1)

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

A Small Molecule Inhibitor of the β-Catenin-TCF4 Interaction Suppresses Colorectal Cancer Growth *In Vitro* and *In Vivo*

Seung Ho Shin [a,b], Do Young Lim [a], Kanamata Reddy [a], Margarita Malakhova [a], Fangfang Liu [c,d], Ting Wang [c], Mengqiu Song [c,d], Hanyong Chen [a], Ki Beom Bae [a], Joohyun Ryu [a], Kangdong Liu [c,d,e,f], Mee-Hyun Lee [c], Ann M. Bode [a,b], Zigang Dong [a,b,c,d,e,f,*]

[a] The Hormel Institute, University of Minnesota, Austin, MN 55912, USA
[b] Program in Bioinformatics and Computational Biology, University of Minnesota, Minneapolis, MN 55455, USA
[c] The China-US (Henan) Hormel Cancer Institute, Zhengzhou, Henan, China
[d] The Pathophysiology Department, The School of Basic Medical Sciences, Zhengzhou University, Zhengzhou, Henan, China
[e] The Collaborative Innovation Center of Henan Province for Cancer Chemoprevention, Zhengzhou, China
[f] The Affiliated Cancer Hospital, Zhengzhou University, Zhengzhou, Henan, China

ARTICLE INFO

Article history:
Received 28 June 2017
Received in revised form 21 September 2017
Accepted 22 September 2017
Available online 27 September 2017

Keywords:
Colorectal cancer
β-catenin
HI-B1
Small molecule inhibitor
Patient-derived xenograft
Precision medicine

ABSTRACT

Colorectal cancer is associated with aberrant activation of the Wnt pathway. β-Catenin plays essential roles in the Wnt pathway by interacting with T-cell factor 4 (TCF4) to transcribe oncogenes. We synthesized a small molecule, referred to as HI-B1, and evaluated signaling changes and biological consequences induced by the compound. HI-B1 inhibited β-catenin/TCF4 luciferase activity and preferentially caused apoptosis of cancer cells in which the survival is dependent on β-catenin. The formation of the β-catenin/TCF4 complex was disrupted by HI-B1 due to the direct interaction of HI-B1 with β-catenin. Colon cancer patient-derived xenograft (PDX) studies showed that a tumor with higher levels of β-catenin expression was more sensitive to HI-B1 treatment, compared to a tumor with lower expression levels of β-catenin. The different sensitivities of PDX tumors to HI-B1 were dependent on the β-catenin expression level and potentially could be further exploited for biomarker development and therapeutic applications against colon cancer.

Home Journals Specialties The Lancet Clinic Global Health Multimedia Campaigns More Information for Submit a Paper

EBioMedicine

Published by THE LANCET

Login | Register |

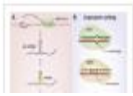
Online First Current Issue All Issues Subject Collections Editorial Team Media Information for Authors

All Content Search Advanced Search

Smartphone-based pathogen diagnosis in urinary sepsis

Barnes et al.

Issue Highlights | Online Now | Most Read | Most Cited



miRNA arm switching identifies novel tumour biomarkers

Liang Chen, Huiyan Sun, Changliang Wang, Yang Yang, Menglei

Why publish in *EBioMedicine*?

- Premium open access venue for translational biomedical research
- Published by The Lancet
- EBioMedicine has an Impact Factor of 6·183*

*2017 Journal Citation Reports®, Clarivate Analytics 2018

Submit Paper

Current Issue

Cover image volume 38, Issue

- **They synthesized a small molecule, referred to as HI-B1with inhibitory effect against β-catenin/TCF4 interaction in colon cancer cells.**

- **HI-B1 : causes apoptosis of cancer cells in which the survival is dependent on β-catenin.**

Synthesis of 4-(5-Fluoro-1H-Benzo[d]Imidazol-2-yl)-N, Ndimethylaniline (HI-B1):

- **To a solution of 4-(Dimethylamino) benzaldehyde in ethanol, Sodium dithionite in water was added.**
- **The resulting mixture was stirred at room temperature for 20 min**
- **then 4-Fluoro-1,2-phenylenediamine was added.**
- **after14 h The solution was diluted with water.**
- **The obtained brown precipitate was filtered and purified from ethanol to give 2.5 g of 4-(5-fluoro-1H-benzo[d]imidazol-2- yl)-N, N-dimethylaniline .**

- **Luciferase Assay, MTS Assay, Flow Cytometry for Analysis of Apoptosis, 7-Day Proliferation Assay, Quantitative PCR (qRT-PCR), Protein Purification ,Immunohistochemistry.**

- **β-catenin is a direct target protein of HI-B1. HI-B1 disrupts the interaction between β-catenin and TCF4 in vitro and ex vivo.**

- **HI-B1 inhibits the growth of tumors with a high expression level of β-catenin, but was not effective against tumors with a low level of β-catenin.**

REFERENCES

- 1. Fumi Takahashi-Yanaga, and Toshiyuki Sasaguri1, The Wnt/β-Catenin Signaling Pathway as a Target in Drug Discovery, J Pharmacol Sci 104, 293 – 302 (2007).
- 2. Roel Nusse, and Hans Clevers, Wnt/b-Catenin Signaling, Disease, and Emerging Therapeutic Modalities, Cell 169, June 1, 2017.
- 3. Kai Kretzschmara,b, Hans Cleversa, Wnt/β-catenin signaling in adult mammalian epithelial stem cells, Developmental Biology 428 (2017) 273–282.
- 4. Hans Clevers and Roel Nusse, Wnt/b-Catenin Signaling and Disease, Cell 149, June 8, 2012 .
- 5. Yann Duchartre, Yong-Mi Kim, and Michael Kahn, Pharmacologic Manipulation of Wnt Signaling and Cancer Stem Cells , Biological Networks and Pathway Analysis, Methods in Molecular Biology, vol. 1613.
- 6. Yung Lyou , Amber N Habowski, George T Chen and Marian L Waterman, Inhibition of nuclear Wnt signalling: challenges of an elusive target for cancer Therapy, British Journal of Pharmacology (2017) 174 4589–4599.
- 7. Dario Zimmerli ,George Hausmann, Claudio Cantù and Konrad Basler, Pharmacological interventions in the Wnt pathway: inhibition of Wnt secretion versus disrupting the protein–protein interfaces of nuclear factors, British Journal of Pharmacology (2017) 174 4600–4610.
- 8. Nithya Krishnamurthy , Razelle Kurzrock, Targeting the Wnt/beta-catenin pathway in cancer: Update on effectors and inhibitors, Cancer Treatment Reviews 62 (2018) 50–60.
- 9. Zachary J DeBruine, H E Xu, and Karsten Melcher, Assembly and architecture of the Wnt/β-catenin signalosome at the membrane, British Journal of Pharmacology (2017) 174 4564–4574.

References

- **10. Clevers, R.N.a.H., Wnt b-Catenin Signaling, Disease,and Emerging Therapeutic Modalities. Cell 169, June 1., 2017.**
- **11. Yu-Feng Xiao, X.Y., Bo Tang, Yong Qin, Jian-Wei Zhang, Dan Zhang, Rui Xie and Shi-Ming Yang, Notch and Wnt signaling pathway in cancer: Crucial role and potential therapeutic targets (Review). INTERNATIONAL JOURNAL OF ONCOLOGY 48: 437-449, 2016.**
- **12. Lorenzi, J.C.C.a.M.V., Drug Discovery Approaches to Target Wnt Signaling in Cancer Stem Cells. Oncotarget 2010; 1: 563 - 566.**
- **13. Mari Masuda a, Masaaki Sawa b, Tesshi Yamada, Therapeutic targets in theWnt signaling pathway: Feasibility of targeting TNIK in colorectal cancer, Pharmacology & Therapeutics 156 (2015) 1–9.**
- **14. Yanqin Lu, X.R., YanzhouWang and Jinxiang Han, Post-translational modifications and secretion of Wnt proteins. Biomedical Journal of Scientific & Technical ResearchVolume 9- Issue 4: 2018.**
- **15. Chenxi Gao, Gutian Xiao, and Jing Hu, Regulation of Wnt/β-catenin signaling by posttranslational modifications, Cell & Bioscience 2014, 4:13.**
- **16. Radu M. Suciu, Armand B. Cognetta, Zachary E. Potter, and Benjamin F. Cravatt, Selective Irreversible Inhibitors of the Wnt-Deacylating Enzyme NOTUM Developed by Activity-Based Protein Profiling, ACS Med. Chem. Lett. 2018, 9, 563−568.**
- **17. Nam-Kyung Lee, Yafeng Zhang, Yang Su, Scott Bidlingmaier, Daniel W. Sherbenou, Kevin D, Ha & Bin Liu, Cell-type specific potent Wnt signaling blockade by bispecific antibody, Scientific Reports (2018) 8:766.**

References

- 18. D.J. Huels, L. Bruens, M.C. Hodder, P. Cammareri, A.D. Campbell, R.A. Ridgway, D.M. Gay, M. Solar-Abboud, W.J. Faller , C. Nixon, L.B. Zeiger, M.E. McLaughlin, E. Morrissey, D.J. Winton, H.J. Snippert, J. van Rheenen & O.J. Sansom, Wnt ligands influence tumour initiation by controlling the number of intestinal stem cells, NATURE COMMUNICATIONS (2018) 9:1132.
- 19. Svitlana Melnik, Dmytro Dvornikov, Karin Müller-Decker, Sofia Depner, Peter Stannek, Michael Meister, Arne Warth, Michael Thomas, Tomas Muley, Angela Risch, Christoph Plass , Ursula Klingmüller, Christof Niehrs and Andrey Glinka , Cancer cell specific inhibition of Wnt/β-catenin signaling by forced intracellular acidification, Cell Discovery (2018) 4:37.
- 20. Seung Ho Shin, Do Young Lima, Kanamata Reddy, Margarita Malakhova, Fangfang Liu, TingWangc, Mengqiu Song , Hanyong Chena, Ki Beom Bae, Joohyun Ryu , Kangdong Liu, Mee-Hyun Lee, A Small Molecule Inhibitor of the β-Catenin-TCF4 Interaction Suppresses Colorectal Cancer Growth In Vitro and In Vivo, EBioMedicine 25 (2017) 22–31.
- 21. http://wires.wiley.com/WileyCDA/WiresArticle/wisId-WSBM1422.html.
- 22. Ethan David Cohen, Ying Tian and Edward E. Morrisey, Wnt signaling: an essential regulator of cardiovascular differentiation, morphogenesis and progenitor self-renewal, Development 135, 789-798, 2008.
- 23. Armando L. Garcia, Adanna Udeh, Karthik Kalahasty, Abigail S. Hackam, A growing field: the regulation of axonal regeneration by Wnt signaling ,2018, Neural Regen Res 13(1):43-52.
- 24. Lina Jansson, Grace Soon Kim, Alan G Cheng, Making sense of Wnt signalinG linking hair cell regeneration to development, Frontiers in Cellular Neuroscience 9(66) 2015.


Thank You